

**Summary Minutes of the Anti-Infective Drugs Advisory Committee Meeting  
November 3, 2011**

**Location: Hilton Hotel Washington DC/Silver Spring, 8727 Colesville Road, Silver Spring,  
Maryland**

**All external requests for the meeting transcripts should be submitted to the CDER,  
Freedom of Information Office.**

**These summary minutes for the November 3, 2011 meeting of the Anti-Infective Drugs  
Advisory Committee of the Food and Drug Administration were approved on January 26,  
2012.**

**I certify that I attended the November 3, 2011 meeting of the Anti-Infective Drugs Advisory  
Committee of the Food and Drug Administration and that these minutes accurately reflect  
what transpired.**

\_\_\_\_\_/s/\_\_\_\_\_  
**Minh Doan, Pharm.D.**  
**Designated Federal Officer**

\_\_\_\_\_/s/\_\_\_\_\_  
**Thomas A. Moore, M.D., FACP**  
**Committee Chairperson**

The Anti-Infective Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on November 3, 2011, at the Hilton Washington, DC/Silver Spring, The Ballrooms, 8727 Colesville Road, Silver Spring, Maryland. Prior to the meeting, members and invited consultants were provided copies of the background material from the FDA. The meeting was called to order by Thomas Moore. (Committee Chairperson); the conflict of interest statement was read into the record by Minh Doan, Pharm.D. (Designated Federal Officer). There were approximately 185 persons in attendance. There were four speakers for the Open Public Hearing session.

**Issue:** The committee discussed clinical trial design issues for the development of antibacterial drugs for the treatment of Community-Acquired Bacterial Pneumonia (CABP) and the draft document entitled "Guidance for Industry, Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment", published March 2009 (see FDA Web site at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064980.htm>).

**Attendance:**

**Anti-Infective Drug Advisory Committee Members Present (Voting):**

Diane Cappelletty, Pharm.D., Dean Follmann, Ph.D., Matthew Goetz, M.D., Thomas Moore, M.D. (Chairperson), Michael Neely, M.D., Kent Sepkowitz, M.D., Melvin Weinstein, M.D., Kathleen Young (Consumer Representative)

**Acting Industry Representative to the Anti-Infective Drug Advisory Committee (Non-Voting):**

John Rex, M.D. (Acting Industry Representative)

**Special Government Employee Consultants (Temporary Voting Members):**

William Calhoun, M.D., Ralph D'Agostino, Ph.D., Thomas Fleming, Ph.D., James Fratzke, D.M.D (Patient Representative), L. Barth Reller, M.D., D.T.M.&H., Allen Roberts, II, M.D., F.A.C.P., Yu Shyr, Ph.D., Bernhard Wiedermann, M.D.

**Regular Government Employee Consultants (Temporary Voting Members):**

John Bennett, M.D., Henry Masur, M.D.

**Guest Speakers Present (Non-Voting, Presenting Only):**

Barry Eisenstein, M.D., F.A.C.P., Thomas File, Jr., M.D., M.Sc., Jeff Dubin, M.D., M.B.A., James Floyd, M.D., M.S., Diana Zuckerman, Ph.D., John Bartlett, M.D.

**Anti-Infective Drugs Advisory Committee Members Not Present:**

Paul Auwaerter, M.D., Archana Chatterjee, M.D., Ph.D., Sheldon Kaplan, M.D.

**FDA Participants (Non-Voting):**

Edward Cox, M.D., M.P.H., John Farley, M.D., M.P.H., Katherine Laessig, M.D., Sumati Nambiar, M.D., M.P.H., Robert Temple, M.D., Thamban Valappil, Ph.D.

**Designated Federal Officer:**

Minh Doan, Pharm.D.

**Open Public Hearing Speakers:**

Gary Noel, M.D. (Vice President and Chief Officer, Paratek Pharmaceuticals), David Friedland, M.D. (Vice President, Clinical Sciences, Cerexa, Inc.), David Shlaes, M.D. (Anti-infectives Consulting, LLC), Roger M. Echols, M.D. (Principal Member, Infectious Disease Drug Development Consulting, LLC)

*The agenda was as follows:*

Call to Order and Introduction of Committee

**Thomas Moore, M.D.**  
Committee Chair, Anti-Infective Drugs  
Advisory Committee (AIDAC)

Conflict of Interest Statement

**Minh Doan, Pharm.D.**  
Designated Federal Officer, AIDAC

**FDA Presentations**

Opening Remarks

**Edward Cox, M.D., M.P.H.**  
Director  
Office of Antimicrobial Products  
(OAP), Office of New Drugs (OND)  
CDER, FDA

Regulatory Background

**Sumati Nambiar, M.D., M.P.H.**  
Deputy Director for Safety  
Division of Anti-Infective Products  
(DAIP), OAP, OND, CDER, FDA

**Guest Speaker Presentations**

Issues in Clinical Trials for CABP

**James Floyd, M.D., M.S.**  
Representing Public Citizen  
Department of Epidemiology  
University of Washington

Community-Acquired Pneumonia Drug  
Studies in Emergency Departments: The  
Perspective from a Practicing  
Emergency Physician

**Jeff Dubin, M.D., M.B.A.**  
Vice Chair  
Department of Emergency Medicine  
Washington Hospital Center

Endpoints and Clinical Trial Issues in  
Community-Acquired Bacterial  
Pneumonia

**Thomas M. File, Jr., M.D., M.Sc.**  
Chair, Division of Infectious Disease  
Summa Health System  
Professor, Internal Medicine; Master  
Teacher; Chair, Infectious Disease  
Section  
Northeast Ohio Medical University

Design of Clinical Trials in CABP

**Barry Eisenstein, M.D., F.A.C.P.,  
FIDSA**  
Senior Vice President  
Scientific Affairs  
Cubist Pharmaceuticals

Antibiotics: A Public Health and Consum  
Perspective

**Diana Zuckerman, Ph.D.**  
President  
National Research Center for Women &  
Families

Community-Acquired Pneumonia

**John Bartlett, M.D.**  
Professor of Medicine  
Johns Hopkins University School of  
Medicine

**FDA Presentations (cont.)**

The Path Forward for CABP Drug  
Development

**Katie Laessig, M.D.**  
Deputy Director  
DAIP, OAP, OND, CDER, FDA

Clarifying Questions to the Presenters

Open Public Hearing

Questions to the AIDAC and AIDAC  
Discussion

**Edward Cox, M.D., M.P.H.**  
Director  
OAP, OND, CDER, FDA

**ADJOURNMENT**

***Questions to the committee:***

1. **DISCUSSION:** Please discuss the merits and limitations of an endpoint based upon improvement in at least 2 of the 4 symptoms of cough, amount of sputum production, chest pain, and difficulty breathing (and no worsening or new symptoms) at day 3 to day 5 as the primary endpoint for Community-Acquired Bacterial Pneumonia (CABP) trials. In your discussion, please comment on a noninferiority margin of 10% for each of the intent-to-treat (ITT) analyses and possibly a 10%, 12.5% or 15% noninferiority margin for the pooled microbiological intent-to-treat (micro-ITT), based on historical data showing a treatment effect on clinical responses noted at day 3 to day 5 of therapy.

*Members generally agreed that an endpoint based upon improvement in 2 of the 4 symptoms [listed above] is valid, but attempts to standardize such a subjective measure are warranted. Members also agreed that clinical signs of disease should not be dismissed from analysis, as they are an objective measure and are complimentary with symptoms in the CABP disease process. From a statistical perspective, it was stated that signs and symptoms should be assessed separately, as a pooled endpoint of the two would obscure results. The committee also discussed the analysis of both the ITT and micro-ITT population. It was agreed that micro-ITT would be a subset analysis, but it was cautioned that when the micro-ITT population falls far below 50% of the ITT, sensitivity is diluted. Several members commented that they would feel most comfortable with a noninferiority margin of 10%, but others could see the rationale for margins of less than 10%.*

*Members also commented on the use of pharmacometrics, which was explained as taking the observed blood levels in patients and translating them into pharmacodynamic estimators by showing the correlation between minimum inhibitory concentration (MIC), plasma exposure, and outcome. However, there was no consensus on the value of the use pharmacometrics, except as supplementary.*

*Please see the transcript for detailed discussion.*

2. **DISCUSSION:** Please discuss the merits and limitations of each of the proposed development pathways and trial designs. In your discussion, please comment on the use of improvement or stabilization of clinical signs of pneumonia as a co-primary endpoint versus its use as a secondary endpoint.

*Much of the discussion for this question was included in the discussion of the first question. The committee felt that all three development pathways appeared reasonable, but members had different preferences. [Please see the slides and FDA backgrounder for development pathways.] Many of the committee members expressed preference for Option #3, but feasibility was a concern.*

*Please see the transcript for detailed discussion.*

3. **DISCUSSION:** Please discuss:
  - a. issues with receipt of prior antibacterial therapy

*The committee agreed that although it would be preferred to enroll patients with no prior antibacterial therapy, the reality is that it is unlikely, so provisions for receipt of prior antibacterial therapy should be made. Members stated that a single dose of a short-acting antibiotic would possibly be acceptable, but a list of short-acting antibiotics should be clearly defined. The effect of the prior antibacterial therapy should be heavily factored into the analysis when determining noninferiority.*

- b. methods to enrich the micro-ITT population

*Several members of the committee mentioned procalcitonin as a tool to enrich the micro-ITT population, but not all members agreed with its use. Other tools including urinary antigen tests, polymerase chain reaction (PCR), and sputum culture were also mentioned.*

- c. mechanisms to overcome barriers to trial conduct

*The committee agreed that the informed consent forms are a major barrier to trial conduct. Streamlining the informed consent process was suggested. It was also mentioned that institutional review boards (IRBs) and Health Insurance Portability and Accountability Act (HIPAA) regulations were impediments to trial conduct.*

- d. any advice on performing clinical trials of oral antibacterial drugs (i.e., when an intravenous formulation is not available).

*Members felt that clinical trials for oral antibacterial drugs would likely be in the outpatient setting or for less severe disease. Members commented that networking community practitioners would be essential to carry out these trials.*

*Please see the transcript for detailed discussion.*

The session adjourned at approximately 5:30 p.m.

